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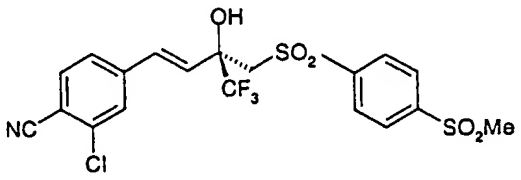

(I)

(57) Abstract

The present invention relates to an (*E*,3*R*)-enantiomer of Formula (I) or a pharmaceutically-acceptable salt or *in vivo*-cleavable ester or ether thereof, substantially free of the enantiomeric (*E*,3*S*)-compound. The compound is a peripherally-selective antiandrogen. The invention also relates to a crystalline form of the enantiomer or the salt, ester or ether thereof. In addition, the present invention relates to a process for the preparation of all of these compounds, a pharmaceutical composition comprising the enantiomer, salt, ester, ether or crystalline form, and uses and methods employing the enantiomer, salt, ester, ether or crystalline form.

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(*E*,3*R*)-ENANTIOMER OF 4-(3-CHLORO -4-CYANOPHENYL) -1-(P- METHYLSULPHONYL -PHENYLSULPHONYL) -2-TRIFLUOROMETHYLBUT -TRANS-3-EN-OL

The present invention relates to an (*E*,3*R*)-enantiomer or a pharmaceutically-acceptable salt, *in vivo*-cleavable ester or ether thereof. The invention also relates to a crystalline form of the enantiomer or the salt, ester or ether thereof. In addition, the present invention relates to a process for the preparation of all of these compounds, a pharmaceutical composition comprising the enantiomer, salt, ester, ether or crystalline form, and uses and methods employing the enantiomer, salt, ester, ether or crystalline form.

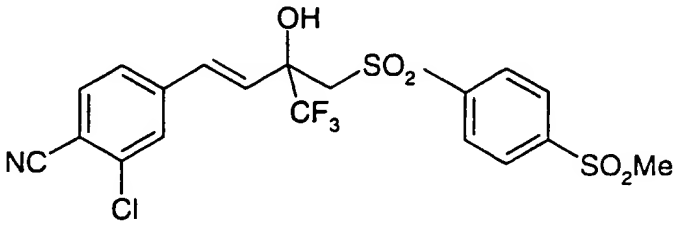
BACKGROUND TO THE INVENTION

Many acylanilides are known which possess antiandrogenic activity. For example, the compounds known as flutamide, bicalutamide and nilutamide have been developed and are used in the treatment of prostate cancer. Such compounds are generally used in combination with an inhibitor of gonadotrophin secretion, for example a luteinising hormone releasing hormone (LHRH) agonist such as goserelin, buserelin, leuprorelin or triptorelin. The properties and usefulness of these antiandrogens have been reviewed, for example in the following documents which are incorporated herein by way of reference :-

flutamide	R O Neri, J. Drug Develop., 1987, 1 (Suppl.), 5-9 and Urology, 1989, 34 (Suppl. 4), 19-21 and United Kingdom Patent Application No. 1360001;
bicalutamide	B J A Furr *et al.*, Urology, 1996, 47 (Suppl. 1A), 13-25, G J C Kolvenbag *et al.*, Urology, 1996, 47 (Suppl. 1A), 70-79 and European Patent Application No. 0100172 as the 8th compound listed in the table in Example 6;
nilutamide	M G Harris *et al.*, Drugs and Aging, 1993, 3, 9-25 and United Kingdom Patent Application No.1518444.

The racemic compound :- 4-(3-chloro-4-cyanophenyl)-1-(p-methylsulphonyl-phenylsulphonyl)-2-trifluoromethylbut-*trans*-3-en-2-ol is disclosed in European Patent

Application No. 0154528 within Example 7 therein and as one of the named compounds in Claim 5. The compound is stated to have a melting point of 172°C and has the structure :-



The correct chemical name of the compound according to the IUPAC Rules of Chemical Nomenclature is believed to be :- 2-chloro-4-[(*E*,3*RS*)-3-hydroxy-4-(4-mesylphenyl-sulphonyl)-3-(trifluoromethyl)but-1-enyl]benzonitrile.

This and the other compounds disclosed in European Patent Application No. 0154528 are stated to possess antiandrogenic properties and to be useful in the treatment of, for example, malignant or benign prostatic disease. There has been no subsequent disclosure of the result of administration of any of these compounds to humans.

It has been observed that administration of flutamide, bicalutamide or nilutamide in single agent therapy to humans causes an increase in the amount of testosterone circulating in the blood. For example, it has been disclosed that administration of bicalutamide leads to an approximate doubling of the basal level of circulating testosterone (G R P Blackledge *et al.*, Urology, 1996, 47 (Suppl. 1A), 44-47). Likewise, it has been disclosed that administration of flutamide causes a 50 to 80% increase in the basal level of circulating testosterone (L Boccon-Gibod *et al.*, J. Urology, 1992, 147, 417A, Abstract 818 and European Urology, 1997, 32, 391-395 and Brufsky *et al.*, Urology, 1997, 49, 913-920). Likewise, administration of nilutamide causes an increase in the basal level of circulating testosterone (A U Decensi *et al.*, J. Urology, 1991, 146, 377-381). It is believed that such increases in the level of testosterone occur when sufficient of the antiandrogen gains access to the CNS and blocks androgen receptors in the hypothalamus. The consequential lack of feedback of the presence of androgen in the body causes the release of LHRH by the hypothalamus which in turn causes release of luteinising hormone (LH) and follicle stimulating hormone (FSH) by the pituitary gland and production of testosterone in the

testis. Aromatase enzyme in fat and other tissues converts some of the increased concentration of testosterone to oestradiol which results in increased concentrations of oestrogen in the blood.

From earlier studies in animals (B J A Furr *et al.*, J. Endocrinol., 1987, 113, R7-9), it was observed that bicalutamide caused a smaller increase in LH and testosterone levels than other acylanilide antiandrogens such as flutamide. It was believed that this lack of an effect was due to the relative lack of access of the compound to the CNS of the animals (S N Freeman *et al.*, Br. J. Cancer, 1989, 60, 664-668). It was therefore anticipated that the compound may have possessed a peripherally-selective antiandrogenic effect. In the event, daily administration of bicalutamide (50mg orally) to a group of patients with advanced prostate cancer gave an overall objective response rate of 70% but also led to an increase in median serum testosterone levels from 10.9 nmol/L to a maximum of 20 nmol/L at week 4 of treatment and a stabilised level of 17.8 nmol/L over the 48 week treatment period (M S Soloway *et al.*, J. Urology, 1995, 154, 2110-2114). Thus the beneficial property of peripheral selectivity in humans has not yet been demonstrated.

It has been stated that certain pyrido[5,6-g]quinoline derivatives provide a peripherally-selective antiandrogenic effect as judged by studies in animals (L G Hamann *et al.*, J. Med. Chem., 1998, 41, 623-639). These results are analogous to the earlier studies of bicalutamide in animals.

The lack of peripheral selectivity of antiandrogenic effect in humans by any of the currently available antiandrogens is disadvantageous, since the resulting increase in circulating testosterone levels requires higher doses of the antiandrogen to be given than would otherwise be the case in order to block access of androgenic compounds to androgen receptors, for example those in androgen-responsive tumour tissue. In addition, the increase in the levels of circulating oestrogen may provide a second disadvantage, in that it may cause one or more of the side effects of gynaecomastia, breast tenderness, hot flushes, impotence, reduction in libido, nausea, vomiting, fatigue and diarrhoea.

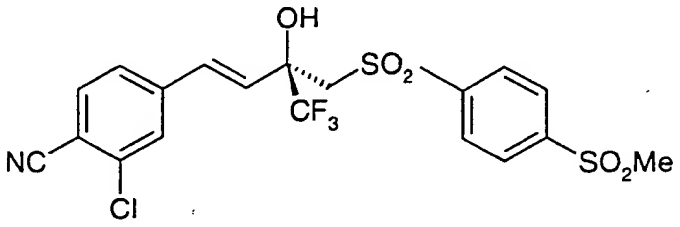
There remains an unsatisfied need for an antiandrogen which overcomes the above-mentioned first disadvantage, and preferably also the second disadvantage. Such a compound would possesses sufficient of a peripherally-selective effect in humans that :-

(i) there would be a smaller increase or no increase at all in the levels of circulating androgens; and preferably additionally

(ii) the incidence and/or severity of one or more of the side effects of gynaecomastia, breast tenderness, hot flushes, impotence, reduction in libido, nausea, vomiting, fatigue and diarrhoea would be reduced.

SUMMARY OF THE INVENTION

The present invention fulfils this need by providing the (*E*,3*R*)-compound of Formula I



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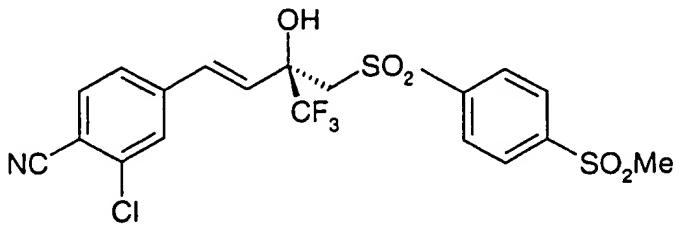
or a pharmaceutically-acceptable salt or *in vivo*-cleavable ester or ether thereof, substantially free of the enantiomeric (*E*,3*S*)-compound.

The present invention also provides a crystalline form of the (*E*,3*R*)-compound of Formula I



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substantially free of the enantiomeric (*E*,3*S*)-compound.

Furthermore, the invention provides a process for the preparation of the (*E*,3*R*)-compound of Formula I, or a pharmaceutically-acceptable salt or *in vivo*-cleavable ester or ether thereof, substantially free of the enantiomeric (*E*,3*S*)-compound.

Another aspect of the present invention relates to a pharmaceutical composition which comprises the (*E*,3*R*)-compound of Formula I, or a pharmaceutically-acceptable salt or *in vivo*-cleavable ester or ether thereof, in association with a pharmaceutically-acceptable diluent or carrier.

A further aspect relates to a pharmaceutical composition which comprises a crystalline form of the (*E*,3*R*)-compound of Formula I in association with a pharmaceutically-acceptable diluent or carrier.

Another aspect relates to the (*E*,3*R*)-compound, salt, ester, ether or crystalline form for use as a medicament.

In addition, the invention relates to the use of the (*E*,3*R*)-compound, salt, ester or ether, or the crystalline form, in the manufacture of a medicament administrable to a patient, for:-

(a) providing a peripherally-selective antiandrogenic effect in the patient; or
(b) providing a peripherally-selective antiandrogenic effect in the patient while suppressing increase in the levels of circulating androgens; or
(c) providing a peripherally-selective antiandrogenic effect in the patient with a reduction in the incidence and/or severity of at least one side effect selected from gynaecomastia, breast tenderness, hot flushes, impotence and reduction in libido obtained when a non-peripherally-selective antiandrogen is used; or
(d) use in the treatment of human prostate cancer, characterised in that a substantially peripherally-selective antiandrogenic effect is obtained and the side effects of gynaecomastia and breast tenderness are induced at a clinically-acceptable level.

The present invention further provides a method of:-

(a) providing a peripherally-selective antiandrogenic effect in a patient; or

(b) providing a peripherally-selective antiandrogenic effect in a patient while suppressing increase in the levels of circulating androgens; or

(c) providing a peripherally-selective antiandrogenic effect in the patient with a reduction in the incidence and/or severity of at least one side effect selected from gynaecomastia, breast tenderness, hot flushes, impotence and reduction in libido obtained when a non-peripherally-selective antiandrogen is used; or

(d) treating prostate cancer in a patient, characterised in that a substantially peripherally-selective antiandrogenic effect is obtained and the side effects of gynaecomastia and breast tenderness are induced at a clinically-acceptable level,

wherein the method comprises administering to the patient the (*E*,3*R*)-compound, salt, ester or ether, or the crystalline form.

FIGURES

FIGURE 1: X-ray diffraction pattern of the (*E*,3*R*)-compound of Formula I;

FIGURE 2: Infra red spectrum of the (*E*,3*R*)-compound of Formula I; and

FIGURE 3: Solid state ^{13}C NMR spectrum of the (*E*,3*R*)-compound of Formula I.

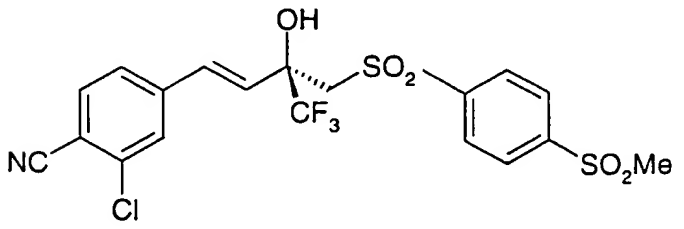
DETAILED DESCRIPTION OF THE INVENTION

As stated above, the side effects of one or more of gynaecomastia, breast tenderness, hot flushes, impotence, reduction in libido, nausea, vomiting, fatigue and diarrhoea may be associated with the administration to humans of effective amounts of currently available antiandrogens. For example, daily administration of bicalutamide (50mg orally) for 4 weeks causes an approximate doubling of testosterone levels and the side effects of gynaecomastia and breast tenderness occur in some patients. According to the present invention we have separated the (*E*,3*R*)- enantiomer of formula I from the racemic compound 4-(3-chloro-4-cyanophenyl)-1-(p-methylsulphonyl-phenylsulphonyl)-2-trifluoromethylbut-*trans*-3-en-2-ol disclosed in European Patent Application No. 0154528

within Example 7, and identified that, surprisingly, this (*E*,3*R*)- enantiomer possesses sufficient peripheral selectivity as an antiandrogenic agent in humans that there is a small increase or no increase at all in the levels of circulating androgens (ie, there is provided a "peripherally-selective antiandrogenic effect in the patient while suppressing increase in the levels of circulating antigens"). This enantiomer preferably also leads to a lower incidence and/or severity of one or more of the side effects of gynaecomastia, breast tenderness, hot flushes, impotence, reduction in libido, nausea, vomiting, fatigue and diarrhoea. In those patients with such side effects, they are preferably induced at a clinically-acceptable level.

The provision of an antiandrogenic effect is useful in the treatment, palliation or prevention of androgen-responsive malignant or benign diseases or conditions such as prostate cancer, prostatitis, benign prostatic hypertrophy or hyperplasia, prostatic intra-epithelial neoplasia, acne, seborrhoea and hirsutism.

The enantiomer of interest is 2-chloro-4-[(*E*,3*R*)-3-hydroxy-4-(4-mesylphenylsulphonyl)-3-(trifluoromethyl)but-1-enyl]benzonitrile, which has the structure shown in Formula I:-



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As explained above, the present invention provides this compound or a pharmaceutically-acceptable salt, *in vivo*-cleavable ester, ether or crystalline form thereof, substantially free of the enantiomeric (*E*,3*S*)-compound. The term "substantially free of the enantiomeric (*E*,3*S*)-compound" as used herein means that the (*E*,3*R*)-compound of Formula I, salt, ester or ether thereof is contaminated with <50% by weight of the (*E*,3*S*)-compound, preferably 10% by weight or less, 5% by weight or less, 2% by weight or less, or 1% by weight or less of the (*E*,3*S*)-compound. Also contemplated, is the optically pure (*E*,3*R*)-compound of Formula I, salt, ester or ether thereof (ie, no contamination with the (*E*,3*S*)-compound).

It will be appreciated that the hydrogen atom of the hydroxyl group of the (*E*,3*R*)-compound of Formula I is relatively acidic by virtue of the electron-withdrawing effect of the adjacent trifluoromethyl group and that, using conventional procedures, the compound may therefore be converted into crystalline pharmaceutically-acceptable salts, for example by reaction with appropriate bases which afford pharmaceutically-acceptable salts, for example an alkali metal (such as sodium and potassium), alkaline earth metal (such as calcium and magnesium) or an ammonium salt or a salt with a sufficiently basic organic amine (which may include an amine such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine and tris(2-hydroxyethyl)amine).

Various forms of prodrugs are known in the art. For examples of such prodrug derivatives, see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and

e) N. Kakeya, *et al.*, Chem. Pharm. Bull., 32, 692 (1984).

Examples of such pro-drugs may be used as guidance to form *in vivo*-cleavable esters or ethers of the (*E*,3*R*)-compound of Formula I. An *in vivo*-cleavable ester of the (*E*,3*R*)-compound of Formula I is, for example, a pharmaceutically-acceptable ester formed by the reaction of the alcohol functional group in the (*E*,3*R*)-compound of Formula I with a conventional pharmaceutically-acceptable inorganic acid or an organic carboxylic acid, or reactive derivatives thereof. Such ester derivatives are cleaved in the human or animal body to release the parent alcohol. Suitable inorganic acids include phosphoric acid and suitable organic carboxylic acids include substituted formic acids such as N,N-dimethylcarbamic acid, alkanoic, benzoic and arylalkanoic acids such as acetic, propionic, benzoic and phenylacetic acid, substituted alkanoic acids such as 2-dialkylaminoacetic and

2-carboxyacetic acid, and substituted benzoic and phenylacetic acids. An *in vivo*-cleavable ether of the (*E*,3*R*)-compound of Formula I is, for example, a pharmaceutically-acceptable ether formed by the reaction of the alcohol functional group in the (*E*,3*R*)-compound of Formula I with a conventional pharmaceutically-acceptable substituted alkyl halide, for example a substituted alkyl chloride or bromide such as an α–acyloxyalkyl chloride, for example acetoxymethyl chloride and pivaloyloxymethyl chloride. Such ether derivatives are also cleaved in the human or animal body to release the parent alcohol.

The size of the dose of the (*E*,3*R*)-compound of Formula I for therapeutic or prophylactic purposes will naturally vary according to the nature and severity of the condition and the route of administration to the patient according to well known principles of medicine. The antiandrogenic effect may be useful for prophylaxis, for example in order to reduce the risk of the inset of prostate cancer in patients. This could be especially useful in men genetically pre-disposed to prostate cancer. Conventional methods are available to classify patients according to their risk of contracting prostate cancer, for example by assessment of family history and measurements over time of particular blood proteins such as prostate specific antigen (PSA).

In using the (*E*,3*R*)-compound of Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, from 10 mg to 7.5 g, preferably from 10 mg to 750 mg, is received (*i.e.* about 0.1 mg/kg to 100 mg/kg body weight, preferably from about 0.1 mg/kg to 10 mg/kg body weight), given if required in divided doses. In general lower doses will be administered if a parenteral route is employed. Typically, unit dosage forms will contain about 10 mg to 500 mg (eg 10mg, 50mg, 100mg or 150mg daily) of the (*E*,3*R*)-compound of the invention, eg for oral administration.

The antiandrogenic potency of the (*E*,3*R*)-compound of Formula I may be determined and compared to that of the (*E*,3*S*)-enantiomer and the corresponding (*E*,3*RS*)-racemate by conventional pharmacological studies in animals such as the determination of seminal vesicle and ventral prostate weights in immature or mature rats according to the methods disclosed by B J A Furr *et al.*, J. Endocrinol., 1987, 113, R7-9. It was determined by

measurement of seminal vesicle weights in mature rats that the (*E*,3*R*)-compound of Formula I possessed outstanding antiandrogenic activity as it was active at a test dose of 1 mg/kg whereas the (*E*,3*S*)-enantiomer did not possess significant activity at a test dose of 10 mg/kg. Accordingly it has been determined that surprisingly the (*E*,3*R*)-compound of Formula I is at least ten fold more potent than the (*E*,3*S*)-enantiomer, which is a further advantage of the invention.

The crystalline form of the (*E*,3*R*)-compound of Formula I is advantageous as there are significant problems associated with the manufacture and formulation (particularly on an industrial scale) of a compound intended for use as a drug which is non-crystalline. Principally, it is problematic to obtain the desired degree of purity in a non-crystalline material, for example if the compound is in the form of an oil, foam or amorphous solid. Moreover, the crystalline (*E*,3*R*)-compound of Formula I possesses improved antiandrogenic potency and a favourable pharmacokinetic profile particularly when the particle size of the compound is relatively small, for example following a conventional micronisation process. The crystalline form of the (*E*,3*R*)-compound of Formula I also possesses improved pharmacological characteristics such as an oral bioavailability allowing for once-daily oral dosing and a lesser degree of inter-patient variation in the ensuing metabolic profiles.

The crystalline form of the (*E*,3*R*)-compound of Formula I can be characterised unequivocally by X-ray crystallography, without the need to refer to data generated using other analytical techniques. Thus, the crystalline form has the following crystal X-ray crystallography data: a = 8.0204(3)Å, b = 10.7796(5)Å, c = 12.0786(3)Å, $\alpha = 90°$, $\beta = 106.351(2)°$, $\gamma = 90°$, and space group = $P2_1$.

Characterisation can also be by means of its X-ray diffraction pattern which gives rise to distinctive peaks [on the 2 theta (θ) scale]. X-ray diffraction data can be obtained using, for example, a Siemens D5000 instrument.

The crystalline form can also be characterised by its melting point. The melting point can be accurately determined using differential scanning calorimetry (hereinafter DSC), for example using a Mettler DSC30 instrument supported by a Mettler TC11 TA processor. The crystalline form melts in the range of 207°C to 210°C. On a differential scanning calorimetry trace the crystalline form has a melting point range corresponding to a sharp peak with an onset of about 206°C.

The crystalline form of the (*E*,3*R*)-compound of Formula I can also be characterised by distinctive peaks in its infra-red spectrum. The infra-red data can be obtained from a 2% weight/weight dispersion of the compound in powdered KBr using, for example, the DRIFTS sampling technique over the frequency range 4000 to 400cm^{-1}.

In addition, the crystalline form of the (*E*,3*R*)-compound of Formula I can also be characterised by other techniques for example using solid state nuclear magnetic resonance spectroscopy, where the crystalline form has distinctive peaks.

The synthesis of the racemic compound 2-chloro-4-[(*E*,3*RS*)-3-hydroxy-4-(4-mesylphenylsulphonyl)-3-(trifluoromethyl)but-1-enyl]benzonitrile can be carried out using the methods described in European Patent Application No. 0154528, which disclosure is specifically incorporated herein by reference. The (*E*,3*R*)-compound of Formula I can be obtained by chromatographic separation of the enantiomers thereof on a suitable chiral stationary phase or by resolution of the enantiomers or of chemical precursors thereof using conventional procedures such as fractional crystallisation, chromatographic separation of diastereoisomeric derivatives (such as the esters formed on reaction of the hydroxy group with a chiral organic carboxylic acid) or asymmetric synthesis from appropriate chiral precursors.

The (*E*,3*R*)-compound of Formula I, or a pharmaceutically-acceptable salt or *in vivo*-cleavable ester or ether thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes are provided as a further feature of the invention and are illustrated by the following representative process variants. Necessary starting materials may be obtained by standard procedures of organic chemistry.

The preparation of such starting materials is described within the accompanying Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

According to this further aspect of the invention there is provided a process for the preparation of the (*E*,3*R*)-compound of Formula I, or a pharmaceutically-acceptable salt or *in vivo*-cleavable ester or ether thereof, substantially free of the enantiomeric (*E*,3*S*)-compound, the process comprising:-

(a) the chromatographic separation of the enantiomers by the elution of a solution of a mixture of the enantiomers in an organic solvent mixture through a chromatography column comprising a chiral stationary phase; or

(b) the fractional crystallisation of a mixture of the enantiomers from a solution thereof in an organic solvent;

whereafter, if necessary, a pharmaceutically-acceptable salt may be prepared by reaction with a base and a pharmaceutically-acceptable *in vivo*-cleavable ester or ether may be prepared by reaction with a carboxylic acid or alkyl halide as appropriate.

A suitable organic solvent for the fractional crystallisation is, for example, a polar solvent such as an alkanonitrile such as acetonitrile, an ether such as methyl *tert*-butyl ether or tetrahydrofuran, a carboxylate ester such as ethyl acetate, a ketone such as acetone or an alcohol such as methanol, ethanol, propanol or isopropanol, or a mixture of a polar and a non-polar solvent, suitable non-polar solvents including an alkane such as hexane, isohexane or heptane or an aromatic solvent such as toluene. Suitable solvent mixtures include mixtures of two polar solvents with a non-polar solvent or mixtures of one polar solvent with two non-polar solvents. A preferred solvent for the fractional crystallisation is acetonitrile.

A preferred fractional crystallisation process comprises forming a concentrated solution of the racemate in a heated suitable organic solvent, cooling the solution to form a supersaturated solution, seeding the solution with one of the enantiomers and allowing the

seeded solution to stand whilst crystals of the seeded enantiomer are deposited. After isolation of the precipitated enantiomer, the mother liquor solution can be reheated to ensure that all seed crystals have dissolved. The concentrated solution can be cooled and seeded with the other enantiomer to allow the deposition of that enantiomer. In a preferred process the solution of the racemate is heated to reflux, cooled to a temperature in the range 10 to 60°C, preferably to a temperature in the range 15 to 45°C, more preferably to a temperature in the range 20 to 35°C, and stored at the selected temperature for a period of between 1 and 36 hours, preferably for a period of between 4 and 24 hours.

Preferably, in option (a) the organic solvent is a 3:1 mixture of ethanol and isohexane, elution through the column being at a flow rate of about 25.4 ml/minute at about 40°C and about 40 bar, and in option (b) acetonitrile is used as a solvent in the solution, and step (b) is carried out by heating the solution in reflux to obtain a clear solution, cooling the solution to about 30°C, seeding the solution with purified (*E*,3*S*)-enantiomer, leaving the mixture to stand at about 30°C for about 15 hours, removing the resulting precipitate, heating the remaining liquor to reflux and obtain a clear solution, cooling the solution to about 30°C, seeding the solution with purified (*E*,3*R*)-enantiomer, leaving the mixture to stand at about 30°C for about 16 hours and isolating the resulting precipitate. Preferably, following option (a) the resulting preparation of the (*E*,3*R*)-enantiomer is further purified by fractional crystallisation comprising dissolving the preparation in acetonitrile by heating the mixture to reflux, cooling the mixture to about 45°C, seeding the mixture with purified (*E*,3*R*)-enantiomer, cooling the mixture to about 20°C while stirring and isolating the resulting precipitate.

The invention also relates to a crystalline form of the (*E*,3*R*)-compound of Formula I obtainable by the process described in the preceding process options (a) or (b).

The composition of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for

example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous or intramuscular dosing) or as a suppository for rectal dosing. Preferably the composition of the invention is in a form suitable for oral use, for example in the form of a tablet or a hard or soft capsule.

The composition of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more flavouring and/or preservative agents.

As stated above, compositions containing the crystalline form of the (*E*,3*R*)-compound of Formula I which are intended for oral use may provide a favourable pharmacokinetic profile, for example suitability for once-daily oral dosing and/or an improved bioavailability of the pharmacologically-active component. In such compositions it is preferable that the particle size of the pharmacologically-active component is relatively small, for example of the size obtainable following a conventional micronisation process.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The method of providing a peripherally-selective antiandrogenic effect in a patient, according to the present invention, may be a sole therapy or may involve, in addition to the administration of the (*E*,3*R*)-compound of Formula I, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment.

For example, when the (*E*,3*R*)-compound of Formula I or the crystalline form is used in the treatment of androgen-responsive malignant diseases or conditions such as prostate cancer and prostatic intra-epithelial neoplasia, it may be normal practice to use a combination of different forms of treatment. The other component(s) of such conjoint treatment may include surgery, radiotherapy or chemotherapy with LHRH agonists (for example goserelin acetate, leuprorelin, buserelin or triptorelin) and/or LHRH antagonists (for example Abarelix).

According to this aspect of the present invention there is provided a pharmaceutical composition for use in the treatment of malignant androgen-dependent disease which comprises the (*E*,3*R*)-compound of Formula I, or a pharmaceutically-acceptable salt or *in vivo*-cleavable ester or ether or crystalline form thereof, and a pharmaceutically-acceptable diluent or carrier in conjunction or admixture with a pharmaceutical composition containing a LHRH antagonist and/or an LHRH agonist.

The peripherally-selective antiandrogenic effect of the (E,3R)-compound of Formula I can be determined by way of clinical studies in humans with measurement of serum levels of testosterone (eg, total or free testosterone). Preferably, other sex hormones, principally oestradiol, LH and FSH can also be measured.

The invention will now be illustrated in the following non-limiting Examples :-

Example 1

Chromatographic separation of the enantiomers

The racemic compound 2-chloro-4-[(*E*,3*RS*)-3-hydroxy-4-(4-mesylphenylsulphonyl)-3-(trifluoromethyl)but-1-enyl]benzonitrile was obtained using the methods described in European Patent Application No. 0154528 (Example 7 thereof). The crystalline (*E*,3*R*)-compound of Formula I and the corresponding (*E*,3*S*)-enantiomer were separated using a group of 8 preparative grade chromatography columns (each of length 8cm and internal diameter 2.6cm), arranged in series and each loaded with a chiral stationary phase

(26 g of Chiracel OJ OOSC HH001 stationary phase per column), using a 3:1 mixture of ethanol and isohexane as eluent at a flow rate of 25.4 ml/minute and with an operating temperature of 40°C and an operating pressure of 40 bar. There were thus obtained various fractions which were enriched in one of the enantiomers and some fractions which contained the separated enantiomers each of approximately 99% purity as determined using an analytical grade HPLC chromatography column (Chiracel OJ 179-073-60216) using a 60:33:7 mixture of ethanol, isohexane and acetonitrile as eluent.

Example 2

Separation of the enantiomers by fractional crystallisation

A mixture of racemate (40 g) and acetonitrile (500 ml) was heated to reflux to obtain a clear solution. The solution was allowed to cool to 30°C and a portion (0.4 g) of the purified (*E*,3*S*)-enantiomer obtained from the chromatographic separation of the enantiomers was added. The mixture was allowed to stand at 30°C for 15 hours. The precipitate was isolated. There was thus obtained the (*E*,3*S*)-enantiomer [2.45 g, 98.3% enantiomeric excess as determined using an analytical grade HPLC chromatography column (Chiracel OJ 179-073-60216) using a 60:33:7 mixture of ethanol, isohexane and acetonitrile as eluent)],
m.p. 207-209°C.

The mother liquors were heated to reflux to obtain a clear solution. The solution was allowed to cool to 30°C and a portion (0.3 g) of the purified (*E*,3*R*)-enantiomer obtained from the chromatographic separation of the enantiomers was added. The mixture was allowed to stand at 30°C for 16 hours. The precipitate was isolated. There was thus obtained the (*E*,3*R*)-enantiomer (1.48 g, 96.7% enantiomeric excess), m.p. 207-210°C.

Example 3

Further purification of the (*E*,3*R*)-enantiomer

Samples from the chromatographic separation of the enantiomers which were enriched in one of the enantiomers were purified further by fractional crystallisation. A sample of the (*E*,3*R*)-enantiomer (1.01 g, 81% enantiomeric excess) was dissolved in acetonitrile (6 ml) by heating the mixture to reflux. The solution was allowed to cool to 45°C and seeded with a portion (0.02 g) of the purified (*E*,3*R*)-enantiomer obtained from the chromatographic separation of the enantiomers. The mixture was cooled further to 20°C and was stirred for 2 hours. The precipitate was isolated. There was thus obtained the (*E*,3*R*)-enantiomer (0.5 g, 99.6% enantiomeric excess).

Example 4

An X-ray structural determination of the (*E*,3*R*)-compound according to the present invention was carried out as follows.

A Nonius ^{Kappa}CCD diffractometer was used (Mo-K_α radiation, $\lambda = 0.71073$Å). Colourless prismatic crystals (0.6 x 0.5 x 0.45 mm^3) were mounted on a thin glass fibre using silicon grease and cooled on the diffractometer to -173°C. The detector to crystal distance was 25mm. Oscillation frames of 5 seconds exposure time with 2° rotation in ϕ were recorded. The data set was completed with additional 2° ω-scans. Integration and scaling of the dataset resulted in a total of 4395 unique data with 2θ less than or equal to 55°. The data were corrected for Lorentz and polarisation effects and for absorption and the structure was solved using direct methods and developed using alternating least squares cycles and difference Fourier synthesis. Refinement converged with $wR_2 = 0.0718$ which corresponds to a conventional R-factor of 0.0294 for data with $I > 2\sigma(I)$. The expected Flack parameter of zero was obtained within experimental error [-0.04(4)].

The structural determination confirmed the structure and showed that the stereochemistry at the asymmetric carbon was (*R*).

The crystal data and structure refinement data were as follows:-

Empirical formula	C19 H15 Cl F3 N1 O5 S2	
Formula weight	493.90	
Temperature	100(2) K	
Wavelength	0.71070 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 8.0204(3) Å	$\alpha = 90°$
	b= 10.7796(5) Å	$\beta = 106.351(2)°$
	c = 12.0786(3) Å	$\gamma = 90°$
Volume	1002.04(6) $Å^3$	
Z	2	
Density (calculated)	1.637 Mg/m^3	
Absorption coefficient	0.460 mm^{-1}	
F(000)	504	
Crystal size	0.6 x 0.5 x 0.45 mm^3	
Theta range for data collection	3.25 to 27.50°	
Index ranges	-9<=h<=10, -13<=k<=14, -15<=1<=15	
Reflection collected	6800	
Independent reflections	4395[R(int) = 0.0366]	
Completeness to theta = 27.50°	99.6 %	
Absorption correction	Scalepack	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4395 / 1 / 285	
Goodness-of-fit on F^2	1.058	
Final R indices [1>2sigma(I)]	R1 = 0.0294, wR2 = 0.0707	
R indices (all data)	R1 = 0.0316, wR2 = 0.0718	
Absolute structure parameter	-0.04(4)	
Extinction coefficient	0.036(2)	
Largest diff.peak and hole	0.269 and -0.321 $e.Å^{-3}$	

Example 5

An X-ray diffraction pattern (Fig. 1) of the (*E*,3*R*)-compound according to the invention was obtained using the following conditions.

An approximately 1g quantity of the compound was placed into a standard Siemens mount and levelled with the aid of a glass microscope slide. The sample, spun at 30 rpm to improve counting statistics, was irradiated with X-rays generated by a: 'copper long-fine focus tube' operated at 40kV and 40mA, wavelength of X-rays - 1.5406Å. The data for the sample was obtained using a standard scintillation detector. The collimated X-ray source was passed through an Automatic Variable Divergence Slit set at V20 (20mm path-length) and the reflected radiation directed through a 2mm anti-scatter slit and a 0.2mm detector slit. The sample was exposed for 4 seconds per 0.02° 2θ increment (continuous scan mode) over the range 2° to 40° 2θ in theta-theta mode. N.B. Running time for the sample was thus 2 hours 6 minutes 40 seconds. Note that the secondary soller slit was left in position. A Dell Optiplex 686 NT 4.0 Workstation operating with Diffrac+ version was used for control and data capture.

The ten most prominent X-ray diffraction peaks in ascending 2θ angle are: 17.1°, 17.3°, 18.1°, 21.2°, 22.4°, 23.1°, 23.4°, 24.2°, 28.2° and 29.5°.

Example 6

The (*E*,3*R*)-compound according to the invention was analysed by differential scanning calorimetry (DSC) using a Mettler DSC 30 and Mettler TC 15 processor. Samples were scanned over the 25°C to 300°C temperature range using a heating rate of 10°C/min. The DSC trace obtained shows one endothermic event. The event is sharp with an onset of 206.7 °C.

Example 7

An FTIR spectrum (Fig. 2) of the (*E*,3*R*)-compound was obtained on a Nicolet 20SXC FTIR Spectrometer from a 2% w/w dispersion of this material in powdered KBr, using the DRIFTS sampling technique, over the 4,000 - 400 cm^{-1} mid-infrared spectral region. Distinctive infrared spectral assignments are:-

3,457 cm^{-1} - O-H stretching vibration of the tertiary alcohol

2,229 cm^{-1} - C≡N stretching vibration of the aryl nitrile group

1,322 cm^{-1} - Asymmetric S=O stretching vibrations of the sulphone groups

1,157 cm^{-1} - Symmetric S=O stretching vibrations of the sulphone groups

965 cm^{-1} - Trans C-H wag vibration of the olefin group

770 cm^{-1} - C-F deformation vibration of the alkyl CF_3 group

574 cm^{-1} - SO_2 scissor deformation vibrations of the sulphone groups

Example 8

The solid state ^{13}C NMR spectrum of the (*E*,3*R*)-compound according to the present invention is shown in Fig. 3.

Example 9

The following illustrate representative pharmaceutical dosage forms containing the (*E*,3*R*)-compound of the Formula I, or a pharmaceutically-acceptable *in vivo*-cleavable ester or ether thereof (hereafter compound X), for therapeutic or prophylactic use in humans:

(a) Tablet I — mg/tablet

Compound X	100
Lactose Ph.Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

(b) Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur	60
Maize starch	7.5
Polyvinylpyrrolidone (5% w/v paste)	30.0
Magnesium stearate	1.5

(c) Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

(d) Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur	488.5
Magnesium stearate	1.5

(e) Injection I	(50 mg/ml)
Compound X	5.0% w/v
1N Sodium hydroxide solution	15.0% v/v
0.1N Hydrochloric acid (to adjust pH to 7.6)	
Polyethylene glycol 400	25.0% w/v
Water for injection to 100%	

(f) Injection II	10 mg/ml)
Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
Polyethylene glycol 400	25.0% w/v

0.1N Sodium hydroxide solution ..... 15.0% v/v

Water for injection to 100%

(g) Injection III (1mg/ml,buffered to pH6)

Compound X ..... 0.1% w/v

Sodium phosphate BP ..... 2.26% w/v

Citric acid ..... 0.38% w/v

Polyethylene glycol 400 ..... 25.0% w/v

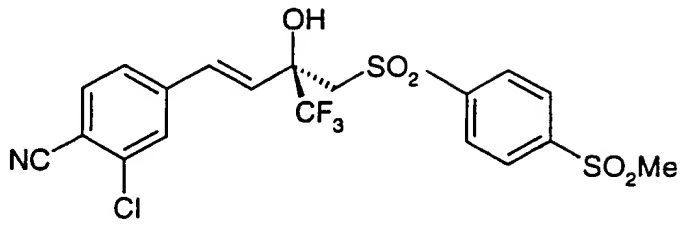
Water for injection to 100%

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

CLAIMS:

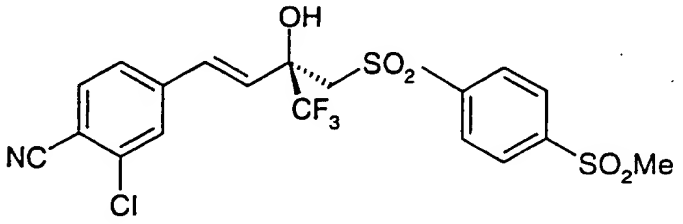
1. The (*E*,3*R*)-compound of Formula I



I

or a pharmaceutically-acceptable salt or *in vivo*-cleavable ester or ether thereof, substantially free of the enantiomeric (*E*,3*S*)-compound.

2. A crystalline form of the (*E*,3*R*)-compound of Formula I



I

substantially free of the enantiomeric (*E*,3*S*)-compound.

3. The (*E*,3*R*)-compound, salt, ester or ether according to claim 1, or the crystalline form according to claim 2, in admixture with 5% by weight or less of the enantiomeric (*E*,3*S*)-compound.

4. A crystalline form of the (*E*,3*R*)-compound of Formula I according to claim 2 or 3, having the following crystal X-ray crystallography data: a = 8.0204(3)Å, b = 10.7796(5)Å, c = 12.0786(3)Å, $\alpha = 90°$, $\beta = 106.351(2)°$, $\gamma = 90°$, and space group = $P2_1$.

5. A crystalline form of the (*E*,3*R*)-compound of Formula I according to claim 2, 3 or 4 having X-ray diffraction peaks on the 2θ scale at about 17.1°, 17.3°, 18.1°, 21.2°,

22.4°, 23.1°, 23.4°, 24.2°, 28.2° and 29.5°.

6. A crystalline form of the (*E*,3*R*)-compound of Formula I according to any one of claims 2 to 5, having a distinctive melting point range of 207°C to 210°C.

7. A crystalline form of the (*E*,3*R*)-compound of Formula I according to any one of claims 2 to 6, having a melting point range corresponding to a sharp peak with an onset of about 206°C on a differential scanning calorimetry trace.

8. A crystalline form of the (*E*,3*R*)-compound of Formula I according to any one of claims 2 to 7, having infra-red spectrum peaks over the frequency range 4000 to 400cm^{-1} at 3457 cm^{-1}, 2229 cm^{-1}, 1322 cm^{-1}, 1157 cm^{-1}, 965 cm^{-1}, 770 cm^{-1}, 574 cm^{-1}.

9. A crystalline form of the (*E*,3*R*)-compound of Formula I according to any one of claims 2 to 8, having peaks on a ^{13}C NMR spectrum at 145.5, 142.6, 141.0, 136.7, 133.2, 130.7, 128.8, 124.6, 123.0, 118.3, 115.3, 113.8, 112.4, 106.3, 96.3, 75.3, 54.8, 48.9 and 45.4.

10. A process for the preparation of the (*E*,3*R*)-compound of Formula I, or a pharmaceutically-acceptable salt or *in vivo*-cleavable ester or ether thereof, substantially free of the enantiomeric (*E*,3*S*)-compound, the process comprising:-

(a) the chromatographic separation of the enantiomers by the elution of a solution of a mixture of the enantiomers in an organic solvent mixture through a chromatography column comprising a chiral stationary phase; or

(b) the fractional crystallisation of a mixture of the enantiomers from a solution thereof in an organic solvent;

whereafter, if necessary, a pharmaceutically-acceptable salt may be prepared by reaction with a base and a pharmaceutically-acceptable *in vivo*-cleavable ester or ether

may be prepared by reaction with a carboxylic acid or alkyl halide as appropriate.

11. The process of claim 10, wherein in option (a) the organic solvent is a 3:1 mixture of ethanol and isohexane, elution through the column being at a flow rate of about 25.4 ml/minute at about 40°C and about 40 bar, and in option (b) acetonitrile is used as a solvent in the solution, and step (b) is carried out by heating the solution in reflux to obtain a clear solution, cooling the solution to about 30°C, seeding the solution with purified (*E*,3*S*)-enantiomer, leaving the mixture to stand at about 30°C for about 15 hours, removing the resulting precipitate, heating the remaining liquor to reflux and obtain a clear solution, cooling the solution to about 30°C, seeding the solution with purified (*E*,3*R*)-enantiomer, leaving the mixture to stand at about 30°C for about 16 hours and isolating the resulting precipitate.

12. The process of claim 11, wherein following option (a) the resulting preparation of the (*E*,3*R*)-enantiomer is further purified by fractional crystallisation comprising dissolving the preparation in acetonitrile by heating the mixture to reflux, cooling the mixture to about 45°C, seeding the mixture with purified (*E*,3*R*)-enantiomer, cooling the mixture to about 20°C while stirring and isolating the resulting precipitate.

13. A crystalline form of the (*E*,3*R*)-compound of Formula I obtainable by the process of any one of claims 10 to 12.

14. The (*E*,3*R*)-compound, salt, ester or ether of claim 1 or 3, or the crystalline form according to any one of claims 2 to 9 and 13 for use as a medicament.

15. A pharmaceutical composition which comprises the (*E*,3*R*)-compound of Formula I, or a pharmaceutically-acceptable salt or *in vivo*-cleavable ester or ether thereof according to claim 1 or 3, in association with a pharmaceutically-acceptable diluent or carrier.

16. A pharmaceutical composition which comprises a crystalline form of the (*E*,3*R*)-compound of Formula I according to any one of claims 2 to 9 and 13 in

association with a pharmaceutically-acceptable diluent or carrier.

17. The use of the (*E*,3*R*)-compound, salt, ester or ether according to claim 1 or 3, or the crystalline form according to any one of claims 2 to 9 and 13, in the manufacture of a medicament administrable to a patient, for providing a peripherally-selective antiandrogenic effect in the patient.

18. The use of the (*E*,3*R*)-compound, salt, ester or ether according to claim 1 or 3, or the crystalline form according to any one of claims 2 to 9 and 13, in the manufacture of a medicament administrable to a patient, for providing a peripherally-selective antiandrogenic effect in the patient while suppressing increase in the levels of circulating androgens.

19. The use of the (*E*,3*R*)-compound, salt, ester or ether according to claim 1 or 3, or the crystalline form according to any one of claims 2 to 9 and 13, in the manufacture of a medicament administrable to a patient, for providing a peripherally-selective antiandrogenic effect in the patient with a reduction in the incidence and/or severity of at least one side effect selected from gynaecomastia, breast tenderness, hot flushes, impotence and reduction in libido.

20. The use of the (*E*,3*R*)-compound, salt, ester or ether according to claim 1 or 3, or the crystalline form according to any one of claims 2 to 9 and 13, in the manufacture of a medicament for use in the treatment of human prostate cancer, characterised in that a substantially peripherally-selective antiandrogenic effect is obtained and the side effects of gynaecomastia and breast tenderness are induced at a clinically-acceptable level.

21. A method of:-

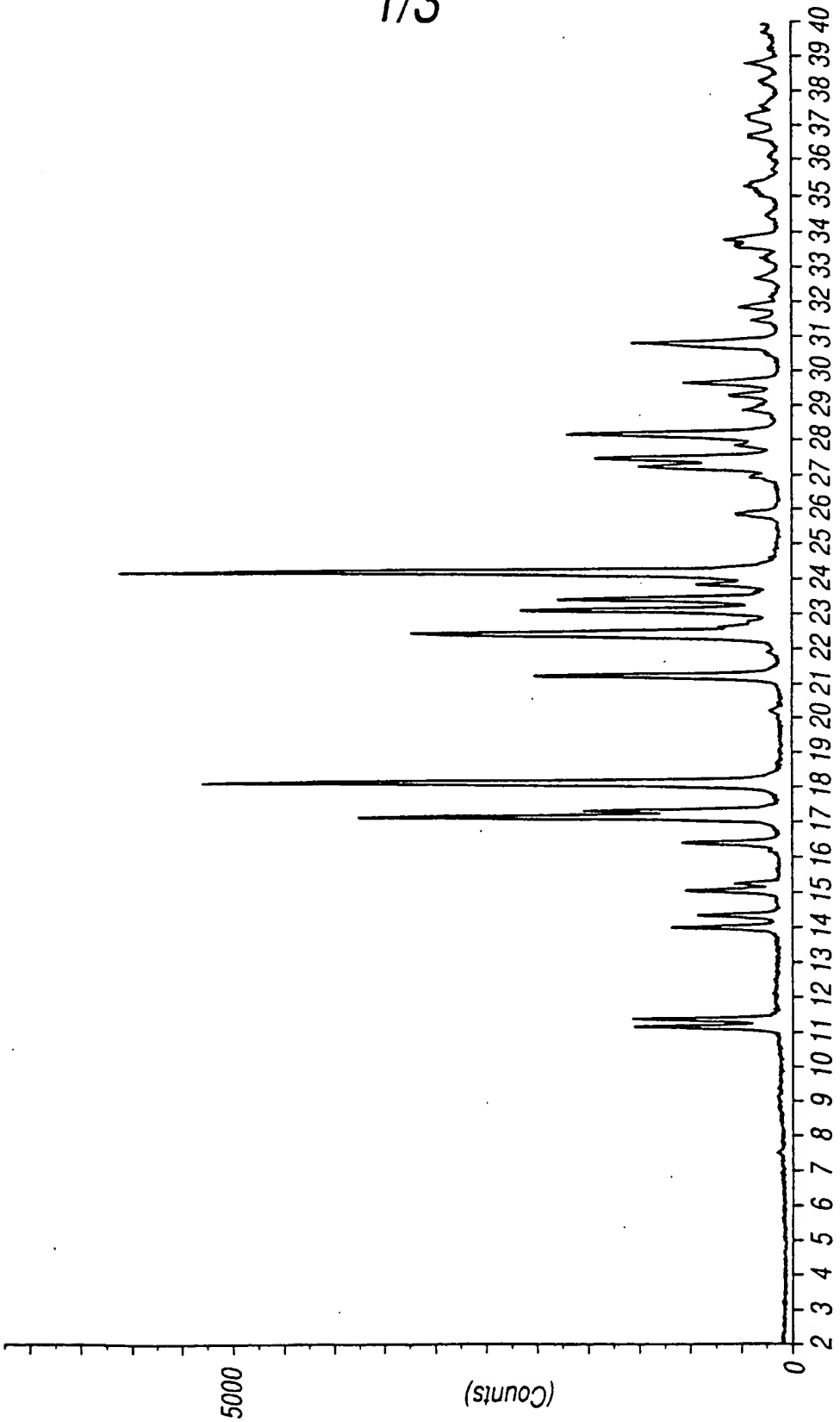
(a) providing a peripherally-selective antiandrogenic effect in a patient; or

(b) providing a peripherally-selective antiandrogenic effect in a patient while suppressing increase in the levels of circulating androgens; or

(c) providing a peripherally-selective antiandrogenic effect in the patient with a reduction in the incidence and/or severity of at least one side effect selected from gynaecomastia, breast tenderness, hot flushes, impotence and reduction in libido; or

(d) treating prostate cancer in a patient, characterised in that a substantially peripherally-selective antiandrogenic effect is obtained and the side effects of gynaecomastia and breast tenderness are induced at a clinically-acceptable level,

wherein the method comprises administering to the patient the (*E*,3*R*)-compound, salt, ester or ether according to claim 1 or 3, or the crystalline form according to any one of claims 2 to 9 and 13.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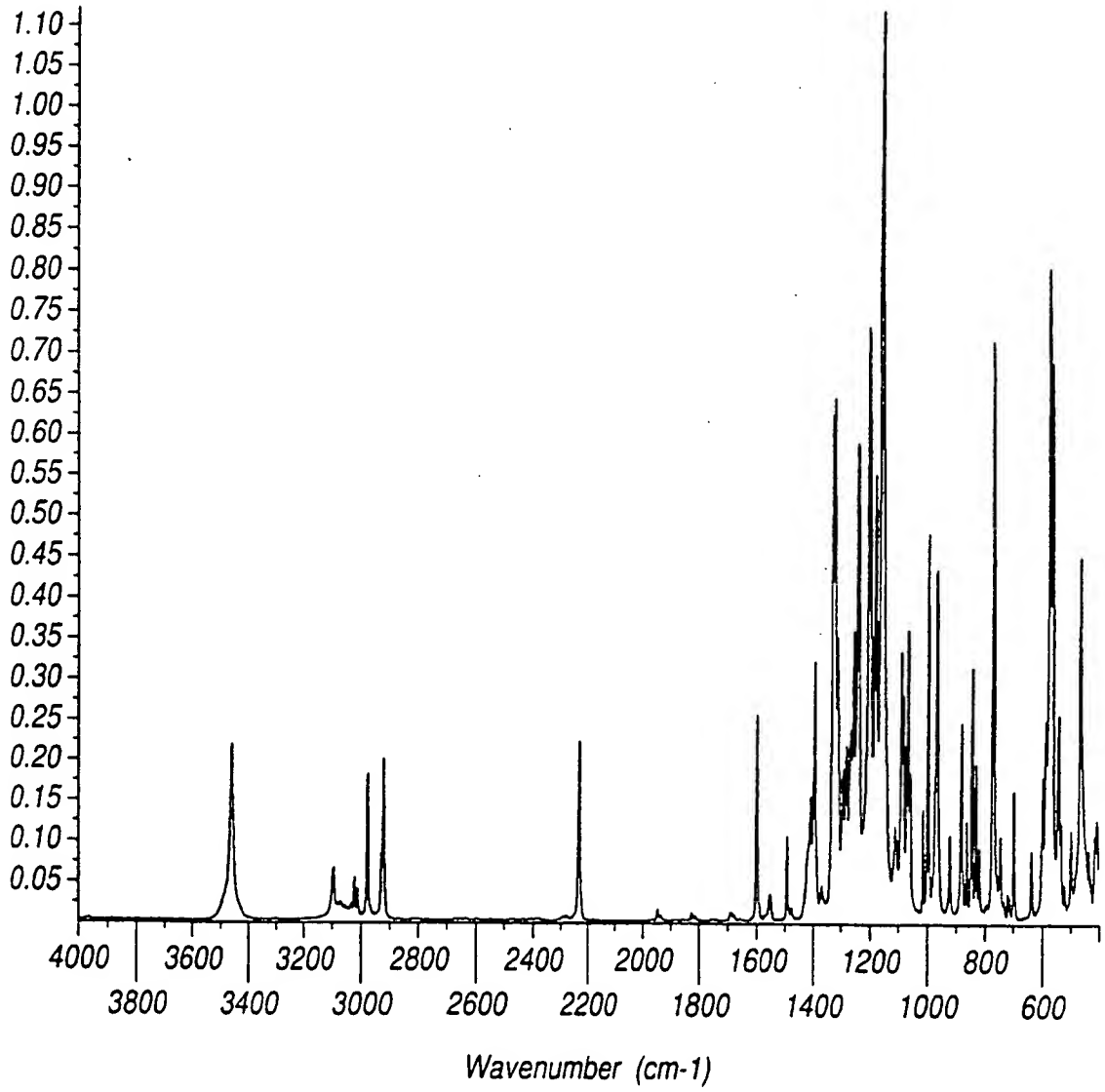
2-Theta-Scale

Fig. 1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0.40
0.35
0.30
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0.20
0.15
0.10
0.05
4000
3800
3600
3400
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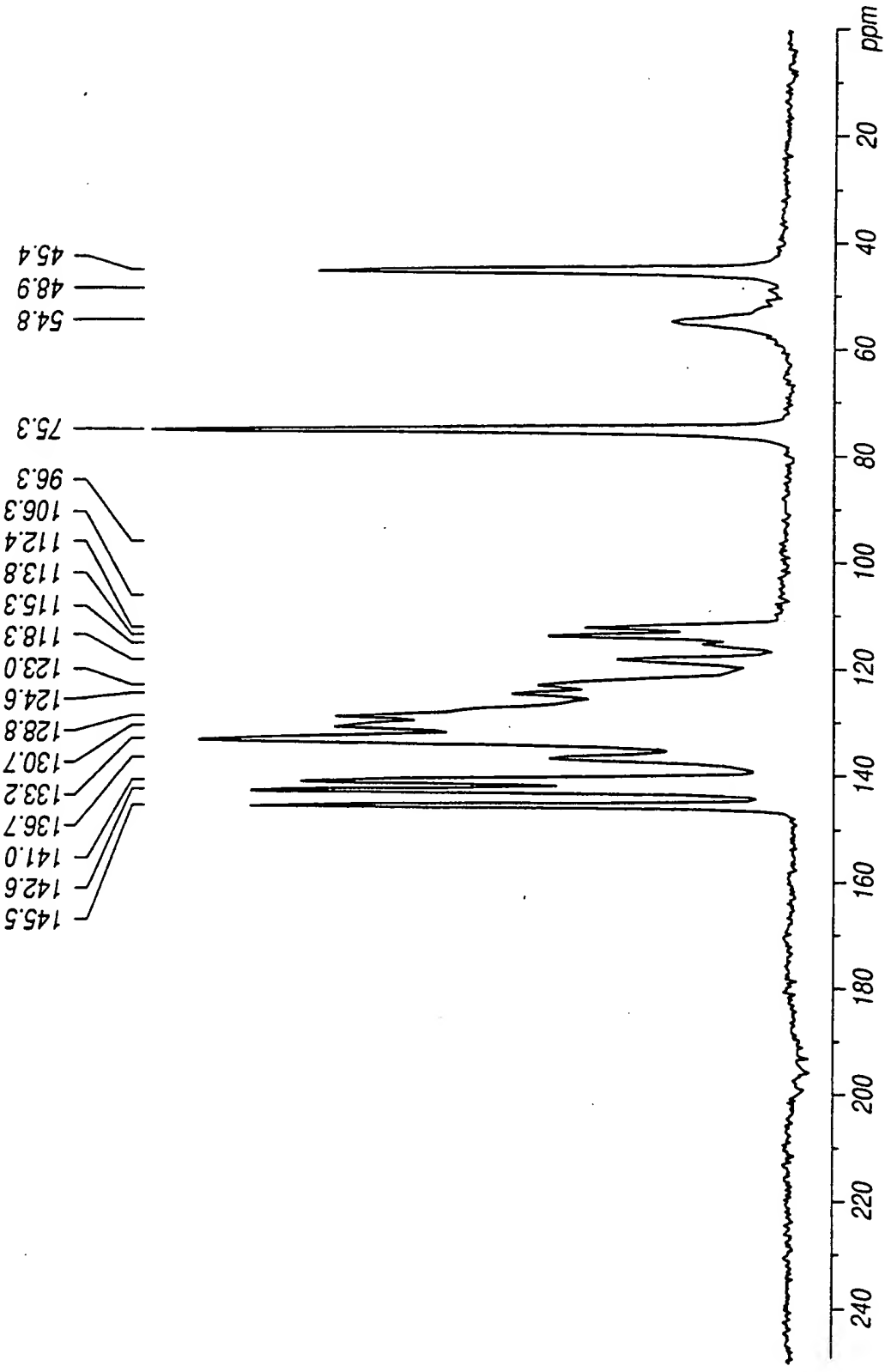
Wavenumber (cm-1)

Fig.2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106.3
112.4
113.8
115.3
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123.0
124.6
128.8
130.7
133.2
136.7
141.0
142.6
145.5

Fig.3

INTERNATIONAL SEARCH REPORT

national Application No
PCT/GB 00/01791

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C317/46 A61K31/275

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 154 528 A (IMPERIAL CHEMICAL INDUSTRIES PLC) 11 September 1985 (1985-09-11) cited in the application page 3, line 34 - page 4, line 15; page 15, line 14 - page 16, line 4; page 33, table entry 12	1,15,17, 21
A	H. TUCKER ET AL: J. MED. CHEM. , vol. 31, no. 4, 1988, pages 885-887, XP000605163 the whole document	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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